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FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

OPEN SESSION

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P A R T I C I P A N T S

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Michael R. Grimmett, M.D., Voting Member
Alice Y. Matoba, M.D., Voting Member

Timothy T. McMahon, O.D., Consultant, deputized to vote
Allen C. Ho, M.D., Consultant, deputized to vote
Anne L. Coleman, M.D., Ph.D., Consultant, deputized to vote
Joel Sugar, M.D., Consultant, deputized to vote
Richard Casey, M.D., Consultant, deputized to vote
Janine A. Smith, M.D., Consultant, deputized to vote
Woodford S. Van Meter, M.D., Consultant, deputized to vote

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FDA:

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A. Ralph Rosenthal, M.D. Director, Division of of Ophthalmic Devices
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Eleanor McGhee

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. WEISS: I would like to call the Ophthalmic Devices Panel to order, and we will have introductory remarks from Sallie Thornton.

Introductory Remarks

MS. THORNTON: Good morning and welcome to the 103rd Meeting of the Ophthalmic Devices Panel. Before we proceed with today's agenda, I have a few short announcements to make. I would like to remind everyone to sign in on the attendance sheets in the registration area just outside the meeting room here.

I just checked, and there are very few signatures, and lots of people in here. So I think there are some folks that need to see Annmarie out there at the registration area.

All handouts for today's meeting are available at the registration table. Messages for the panel members and FDA participants, information or special needs, should be directed through Ms. Annmarie Williams or Mr. Hashim Khalif, who are available in the registration area.

The phone number for calls to the meeting area is 301/977-8900. In consideration of the

panel, the sponsor, and the agency, we ask that those of you with cell phones and pagers either turn them off or put them on vibration mode while in this room. We're serious about this.

We ask that all meeting participants speak into the microphone and give your name clearly so that the transcriber will have the accurate recording of your comments. All available information for the meeting tentatively scheduled for March 14-15 will be on the FDA Advisory Committee website in approximately one week.

Now, at this time, I would like to extend a special welcome and introduce to the public the panel and the FDA staff two panel consultants who are with us for the first time today and our new panel consumer representative.

Dr. Richard Casey comes to us from Los Angeles--there he is--where he is an Associate Professor of Ophthalmology at the Jules Stein Eye Institute and the Interim Chairman of the Department of Ophthalmology at the Charles Drew University of Medicine and Science.

His clinical practice involves the management of the corneal and anterior segment disease, cataract and refractive surgery.

Dr. Janine Smith is the Deputy Clinical Director of the National Eye Institute of the National Institutes of Health in Bethesda, Maryland. Her basic science research has been immune-based disease of the ocular surface with additional responsibilities for the NEI intramural clinical research program.

And Ms. Glenda Such, the consumer representative to the panel, is the Director of Computer Training Programs in the Department of Career Services at Lighthouse International in New York City. She is a recognized expert in the field of adaptive technology for visual impairments and the functional implications of visual disabilities, particularly low vision.

We very much appreciate your commitment to serve and welcome you to the panel table today.

To continue, will the remaining panel members please introduce themselves beginning with Dr. Van Meter?

DR. VAN METER: Woodford Van Meter, University of Kentucky in Lexington, Kentucky, practice in corneal and external disease.

DR. HO: Allen Ho, Philadelphia, Thomas Jefferson University, Wills Eye Hospital.

DR. COLEMAN: Anne Coleman, Associate Professor, glaucoma specialist at UCLA, Los Angeles.

DR. GRIMMETT: Michael Grimmett, University of Miami, Bascom Palmer Eye Institute.

DR. WEISS: Jayne Weiss, Professor of Ophthalmology and Pathology at Kresge Eye Institute, Wayne State University, Detroit.

DR. BRADLEY: Arthur Bradley, Professor of Visual Sciences, Indiana University.

DR. MATOBA: Alice Matoba, Associate Professor at Baylor College of Medicine.

DR. McMAHON: Tim McMahon, Professor and Director of the Contact Lens Service at the University of Illinois in Chicago.

DR. SUGAR: Joel Sugar, University of Illinois in Chicago.

DR. ROSENTHAL: Ralph Rosenthal, Director of the Division of Ophthalmic and Ear, Nose and Throat Diseases, FDA.

MS. THORNTON: Thank you. I would like to note for the record that at the sponsor's request, the panel industry representative, Mr. Ronald McCarley, will not be at the table today. Therefore, the change will necessitate a slight

correction in today's agenda. The comments of the industry rep that are requested following the voting will not be included. Mr. McCarley will return to the table for Friday's proceedings.

With the chair's permission, I would now like to proceed to read the Conflict of Interest Statement for this meeting and the Appointment to Temporary Voting Status for the Panel Consultants.

Conflict of Interest Statement

MS. THORNTON: The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The agency has no conflicts to report for today's agenda. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest,

the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Appointment to Temporary Voting Status

MS. THORNTON: The Appointment to Temporary Voting Status. Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on January 17, 2002: Drs. Allen Ho; Timothy McMahon; Joel Sugar; Anne Coleman; Richard Casey; Janine Smith; and Woodford Van Meter.

In addition, I appoint Dr. Jayne Weiss to serve as acting panel chair for the duration of this meeting.

For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical

Devices Advisory Committee. They have undergone the customary conflict of interest review, and have reviewed the material to be considered at this meeting.

Signed, Dr. David W. Feigle, Director, Center for Devices and Radiologic Health, January 9, 2002.

Thank you.

OPEN PUBLIC HEARING

DR. WEISS: Thank you, Sallie. This now closes this portion, and we're going to continue on to the Open Public Hearing. If anyone has any comments to make, they need to come up to the podium, identify themselves, and any financial conflicts or potential conflicts that they may have.

OPEN COMMITTEE SESSION

DR. WEISS: Seeing no one approach the podium, we will close the public hearing session and move on to the committee session and begin with the FDA Division Update. Dr. Rosenthal. I'm told that Donna Lochner, Chief of the Intraocular and Corneal Implants Branch, has the update.

Branch Updates

MS. LOCHNER: Thank you. I have one

announcement of a personnel nature, and that is Ashley Boam, a biomedical engineer in the Intraocular and Corneal Implants Branch, has been temporarily reassigned to the Office of the Commissioner in FDA. She has accepted this six-month assignment in the Office of Planning and Legislation and is working primarily on the Prescription Drug Users Fee Act.

We anxiously await her return in July and I'll note that while she is reassigned, she will, however, continue her responsibilities representing FDA on the ophthalmic standards committees, perhaps most notably and importantly the phakic IOL standard committees.

Thank you.

PMA P010059

DR. WEISS: If there is no other information to be updated from the agency, I would like to move ahead to discuss and review the sponsor's PMA P010059. We will begin with the sponsor presentation. The sponsor can approach the podium and there is one hour.

I would like each presenter for the sponsor to first identify themselves at the beginning of their presentation.

SPONSOR PRESENTATION

DR. STEINERT: Good morning. My name is Dr. Roger Steinert. I am not the medical monitor on this study. Dr. Howard Fine is the medical monitor. I want to just explain a few things. I have no financial interest in this product. I am not paid to be here. I have never received a cent from Morcher and I never will, as far as I know.

I am here because I was one of the investigators, and Dr. Fine could not be here today. I felt that it was extremely important that we try to focus on the clinical aspects of this implant, how it works, and the results, and when Mr. Welch asked me if I would pinch hit for Dr. Fine, I agreed.

The first time that I saw the data at all was mid-December. So I have put about 50 to 100 hours into this over the holidays and the past couple of weeks, trying to bring this into a form that made sense to me as a surgeon and as a clinician, and I want to convey that to you.

So if the format here is a little different than you might be used to, that's the reason for this.

I'd also like to take this opportunity to

thank Ms. Thornton and Ms. Lochner and Mr. Glover and Dr. Lepri from FDA and especially Dr. Sugar and Dr. Van Meter, who were the primary reviewers.

I know that the submission was not as clean, to put it mildly, as you would like, and this has been a kind of a difficult task for you, and we are very appreciative of the support you have given to Mr. Welch in allowing us to finally get to this day of presenting to the FDA, so thank you very much.

I think it would be helpful to start with the description of the capsular tension ring itself, and just give you a little bit of background.

This device was invented a little over ten years ago by Dr. Witschel in Germany. And the purpose has always been in my mind one thing and one thing dominantly, and that is to enhance the mechanical stability of the lens capsule in the presence of weak or absent zonules. That's it. There's been a lot of other stuff connected to this that I think is inappropriate and we're not going to pursue any of those other things. This is what this device is for.

So how does it work? Well, the basic

mechanical concept is recruitment of adjacent zonules. When you have weak zonules or missing zonules, the idea is to mechanically interconnect other zonules at the equator so that the neighboring zonules provide more support than they would otherwise.

Now, I'm going to show you a brief video clip here, and you'll see this is a surgical tape of a phako, and you can see that there are weak zonules--they're not completely absent--to the right on that screen, and you can see how the equator is visible out here at the edge, and you're going to see a brief edited video with phakoing and then implementation of the ring, and you will see the shift in the position of the capsular bag as a result of that.

This is the ring itself going in. It's a very simple device, very thin piece of PMMA. This is a manual insertion. There's also a shooter insertion which I use regularly. It makes life a lot easier. And you see as it goes around, you can see how that equator is now closer to the normal position. It's not perfect. This device does not recreate zonules. It simply recruits mechanical stability from the adjacent zonules.

So now the ring is in place. I think that was just to demonstrate the position of it by the surgeon, and now we've got a one piece PMMA lens in, and you'll see a before and an after to emphasize that the position of the capsular bag is improved by the presence of the ring and the presence of the implant.

So that's basically how it works. Now the next slide is a Meoki [ph] presentation. This is a normal cadaver human eye seen from the posterior side so it's a Meoki view, and you'll see a few things within this. First, this is just the standard posterior view, and in just a moment, we'll get a close up of what's going on in the periphery.

You can see zonules out there attached to the capsular bag running this way. Those are the two little eyelets, the beginning and the end, and typically there's a little bit of a space, the relationship of the implant to it.

Now, the purpose of this is to demonstrate why--the one thing you'd fear is that this thing would poke through the capsular bag during insertion. You can see actually those ends can be pressed fairly hard against the equator without

puncturing, and that's the purpose of that little demonstration.

So that's it. That is what this is all about. Now, a brief history of Morcher. It was founded in 1943 as a manufacturer of contact lenses. It began as an IOL manufacturer in 1955 so they've been in this business for a long, long time. It's the Dannheim lens in 1955 and then working with Binkhorst as early as 1958.

In 1981, to the best of my knowledge, they were the first IOL manufacturer to use gamma sterilization to improve the biocompatibility and reduce toxicity in IOL sterilization.

In 1987, they developed something that they called the compression forge method, which is the thing that I am told allows them to create these rings so that they have a high degree of fracture resistance with a very flexible PMMA.

They distribute internationally throughout the world, and as far as I know, they have an excellent track record with the ring, and it is consistent with the highest standards of manufacturing quality.

In my personal opinion, there is one indication for the use of the capsule tension ring,

and that is stabilization of the crystalline lens capsule in the presence of weak or absent zonules. I'm a believer in keeping things simple, and I think this is what this is all about. Trying to attach other things to this that cannot be substantiated in any easily done clinical study I think is a mistake, and I am told that Morcher and the sponsor are in agreement this is the one indication that we are looking for approval for today.

I think typical conditions as guidance to a clinician would be patients with pseudoexfoliation, prior trauma, prior pars plana vitrectomy, and Marfan's Syndrome, but it's not limited to that.

Now, the IDE, as many of you know, and the rest of you will hear several times today, occurred in several phases. Phase I was the original study. 11 surgeons at five sites who are referred to as the core group were allowed to enroll 75 eyes, and there has now been a minimum two-year follow-up period on most but not all of those patients.

There has been difficulty with follow-up because a lot of these patients are referred from a distance and it is impossible to extract

information out of the following originating ophthalmologists at a distance in some cases.

This is the core group. Dr. Fine, as I mentioned, is the medical monitor; Dr. Garbow; Dick Lindstrom's group in Minneapolis; Bobby Osher's group in Cincinnati; and myself.

Now, Phase II had two groups. One was the same core group allowing additional enrollment. Ultimately, in Phase II were 202 patients and 240 eyes. And further independent investigators, ultimately totaling 43, who were begging for the ability to use this device for patients who needed it, were allowed to implant under the auspices of this sponsor's study 204 patients and 225 eyes.

There is a Phase III. Now you won't be hearing data on this because this is not part of the submission and wasn't required, but you should know that the core group of investigators has been allowed to do limited ongoing implantations for patients who need it and that has resulted in 54 further implants at four sites.

So, first I'd like to talk about efficacy. I think the appropriate primary measures of these: does it help the IOL center; is it stable in the long term; and does it reduce vitreous loss at

surgery? These are very high risk patients by and large who are at risk for vitreous loss.

So let's talk about each of these in turn. IOL centration. Well, I asked about reportable clinically detectable decentration. And let me say right up front, this is a real problem if you've approached this in a rigid scientific way. We don't have great methodology for determining IOL centration. And I don't believe any of the IOL studies submitted by other sponsors just for conventional IOLs where they talk about centration do anything differently.

It's very subjective. I'd love to see a practical clinical test that we could export to the field that would allow us to really figure out where the center of an implant is and measure it at a millimeter level of accuracy, but we don't have it, and it is absolutely true that as long as you can't see something shifting in the pupillary zone, you won't know whether it's moved.

So could these rings be moving one or two millimeters? Could the implant be moving one or two millimeters? Yes. Without detection? Absolutely. And when the investigator says it's one millimeter decentered, how do they determine

that? They don't have digitized photos. We know that. This is the world we live in.

This is as best as we can do is to ask the surgeons do they see detectable decentration? So in Phase I, the core group, five out of 50 of the reported patients at two years, were reported to have some clinically detectable decentration. In Phase II, the core group was 12 out of 157 at one year, which was the requested follow-up interval resulting in a rate of 7.6 percent, and for the independent investigators in Phase II, it was seven out of 109 at one year, or 6.4 percent, reporting some clinically detectable decentration.

What about long-term stability? There were nine reports of decentration of IOLs, and at the last report, one of them was said to be two millimeters and eight eyes were said to be one millimeter or less. That's the total number of reports of decentered IOLs. Now, I don't believe that that's the total amount of decentration at any level.

But this is what the surgeons reported and so it must be what they perceive as at least clinically detectable.

There have been no reports of extrusion of

the ring from the capsular bag. It stays in the bag.

What about vitrectomy? You have to remember these are high risk patients with bad zonules, and we don't know. Unless somebody does a prospective randomized study, nobody will know what the incidence of vitrectomy will be with and without the ring.

So the best we can say is that the expected incidence approaches 100 percent. Core group, Phase I, eight out of 75, or 13.3 percent. Core group, Phase II, 19 out of 240, or 7.9 percent. And independent investigators Phase II, 17 out of 225, or 7.6 percent.

What about visual acuity issues? Well, we're going to talk about visual acuity under safety, but visual acuity is not an appropriate efficacy outcome measure of the capsule tension ring. That's not what this ring does. It's not an intraocular lens. And comparison of the results to the FDA grid for our results is irrelevant.

The cases in which the ring are implanted, and I'm sure you all understand this, are selected for a high degree of pre-op pathology and intra-op pathology. These are high risk patients.

So let's talk about safety. I think the primary measures were these: stability after YAG laser capsulotomy; evidence of inflammation; explantations; people who had best corrected visual acuities less than 20/40; and other relevant post-op pathology. So we'll address each of those in turn.

Stability after YAG laser capsulotomy. We went through and pulled out reports of anything that was report of more decentration after YAG capsulotomy than before YAG capsulotomy, and we found three reports of possible new or increased decentration.

And this is what we have to deal with for reports from the doctors. One eye was reported as slight pre-YAG, whatever slight means. The YAG was done at four months post-op, and all the post-op reports report the IOL as being two millimeters decentered. It has not required reoperation.

One eye was reported as one millimeter decentered at the first report after YAG at 10 to 14 weeks. All subsequent reports failed to report any decentration on that eye.

And one eye had a very complex procedure with cutting of vitreous strands with the YAG laser

and an anterior capsulotomy at seven weeks. Decentration was reported as two millimeters at ten to 14 weeks, one-half millimeter at 22 to 26 weeks, no decentration 11 to 13 months, and one millimeter at 23 to 25 months.

And those are the only reports of any change in position after YAG capsulotomy. And again, no cases of extrusion of the ring after laser capsulotomy.

What about inflammation? Well, the FDA has raised issues of biocompatibility of the PMMA used in the ring. So we looked at possible correlations with reports of inflammation, and if you look at iritis, the incidence, any occurrence, it was six patients, or 1.2 percent, reported as having iritis at any post-op interval; zero at the last reporting interval.

And for CME, there's 11, or 2.1 percent, incidence at any time, and four, or .76 percent, persisting at the last reporting interval.

Frankly, I'm stunned that it's that low. These are very complicated cases. A lot of vitrectomy is being done.

Now, technical problems with the ring. There were 540 total implants. Three were reported

as having broken eyelets. As I said, none were reported as extruding post-op. No surgeon felt that there were complications attributable to the ring. There were no infections, and there were no adverse events that the surgeons felt were attributable to the ring.

There were four cases where the ring could not be fixated in the bag at the time of surgery. And therefore it was not left in the eye.

So let's talk about ring explantations. Again, 540 total implants. There were eight explanations for a rate of 1.5 percent. Seven of those eight were during the primary surgery. Two of them were due to procedural issues. Four of them I've already referenced were due to inadequate capsule or zonules to support the ring, and one was because the surgeon didn't feel it was the correct ring size.

There are three slightly different sized rings depending on level of myopia and the size of the capsular bag.

And there was one post-op explanation. It was a reintervention at one week post-op. The ring along with the IOL was removed due to the judgment that the whole capsular complex was unstable.

Again, I want to emphasize as somebody who has used this, this doesn't manufacture zonules. And there absolutely are people who have way to few zonules for this ring to rescue their situation. So there is surgical judgment involved, and it's a learning curve, and sometimes you put it in, and it doesn't work. There's always that potential.

Now, let's talk about retinal detachments. In Phase I core, there were three RDs; in Phase II core, five retinal detachments reported; and the independent investigators reported no retinal detachments.

Of those eight detachments, five were present pre-op; two were detected immediately post-op, at the first post-op interval. It is unclear, but raises the question as to whether these were also present pre-op. And there was one that definitely occurred post-op at the two year post-op interval.

Other major posterior pathology is as follows: early phthisis was reported in one patient. We went back and looked at that. That was a patient who had one of these pre-op total retinal detachments and light perception vision. The lens had been removed in order to visualize the

retina to see whether it could be repaired. The patient never did get reattachment of the retina and eventually started to fade into phthisis at the last report.

One patient had a vitreous hemorrhage that was present post-op, and one patient was reported as having a branch retinal vein occlusion. It was not there at the one to two week report and at the 10 to 14 week, it was, and it was detected due to the drop of best corrected acuity from 20/25 to count fingers. And the surgeon did not think there was any plausible connection between the branch retinal vein occlusion and the presence of the ring.

Now what about the people who lose, not even necessarily lost, but let's say failed to gain acuity at the level of 20/40 or better? So these are people whose post-op best corrected acuities were less than 20/40.

In yellow, we have the raw number, and then white is percentages. And you can see that the highest levels were for age-related macular degeneration. And then other macular issues. Typically that was things like traumatic maculopathy and epiretinal membranes.

Some of these were the retinal detachment patients. There are a fair number who had posterior capsule opacity, but had not undergone YAG capsulotomy at the time of the reporting interval. Some with irregular corneas, largely dryness. Allegedly, only a couple of CMEs responsible for less than 20/40. One patient with optic atrophy. A couple of people who were said to have severe glaucoma. Two with diabetic maculopathy, and then a very small number of miscellaneous patients.

What about glaucoma? Well, glaucoma was reported by two in Phase I, nine core patients in Phase II, and six of the independent investigators.

All of the Phase I core patients reporting glaucoma, it was preexisting preoperatively. And Phase II, eight of the nine had preexisting glaucoma. One of the nine was an acute post-op pressure elevation that was treated, and the glaucoma in this case, the definition was IOP requiring medication. So this was reported, but it was only the first post-op day and was gone thereafter.

In the Phase II independent patients, two of them it was preexisting. One it was first day

post-op only. Two were early post-op only, and then there was one lost to follow-up--and one of those two were lost to follow-up, and then one we're pending longer follow-up reports on and have not received it from the independent investigator.

These are the worldwide sales of the capsule tension ring. I thought this would be interesting to you to get a sense of how often or more precisely how infrequently the ring is used.

These are sales. No one has figures on actual implantation. So you could guess maybe 50 percent of these actually get implanted. And you can see when you consider worldwide cataract surgery of many millions a year, this is not a large number. This is a device restricted to patients who are very specific and have a very unusual but very needy condition.

So, in conclusion, the Morcher capsule tension ring has been in use for a decade internationally. It's available throughout the world. It enjoys consistently positive clinical reports, absence of complications attributable to the ring, and a track record of long-term stability and biocompatibility throughout the world.

The U.S. clinical trials under this IDE, I

think, reflect the positive experience that has been present worldwide with the Morcher ring. The capsule tension ring in my opinion effectively stabilizes the capsular bag in cases of weak or partially absent zonules, and it reduces the rate of serious complication such as vitreous loss, dislocation of the nucleus posteriorly and inability to implant a PC IOL.

No safety concerns about the ring have arisen in the course of this trial, and there is no alternative device or technique to achieve these clinical objectives. Thank you very much for your attention.

DR. WEISS: If that ends the sponsor's presentation, Dr. Steinert, I'll ask you to stay at the table, and we'll have 15 minutes of questions from the panel for you, and then we'll have the FDA presentation.

Panel Questions for the Sponsor

DR. WEISS: Dr. Sugar.

DR. SUGAR: Thank you, Jayne. This is Joel Sugar. I'd like to thank Roger for his candor. I have a bunch of questions and stop me if these are out of the range of what I'm supposed to ask now.

First of all, the indications for implanting the lens and the numbers of patients are things that have confused me throughout my review of the data that's been presented and represented.

And Roger just presented in Phase II, I guess, two independent, that there were 225 eyes and 204 patients. The information presented to me said that there were 241 eyes and 215 patients. I can understand if the cutoff date or the date of freezing of the data was changed, that the numbers would increase. I can't understand the numbers decreasing.

I assume that we work under the principle that once randomized, once assigned in a study, always analyzed. So I guess if you could begin with that.

MR. WELCH: When we did the revision, in order to--

MS. THORNTON: Excuse me. Could you identify yourself, please?

MR. WELCH: Certainly, sorry. My name is Hillard Welch. I am the U.S. representative for Morcher, Stuttgart, Germany. When we did the revision of the statistics and the data, we did it against a different date, and the original

submission was a random one unfortunately. That was my error in compiling it because I picked different dates when I shut off various parts of the tabulation.

And we finally settled on a date of October 1, and all of those figures that you're now referring to, the 225 and the 204, are based on that date, and the data that had been received as of that date. So that is the figure you should use and not the preceding one.

DR. SUGAR: So the number got smaller because some in the original submission didn't--

MR. WELCH: Yeah, they should not have been included--

DR. SUGAR: --submit an update.

MR. WELCH: --in part because when the tabulation was originally done, it picked up a variant of the ring which is not included in this study.

DR. SUGAR: Thank you. Can I continue?

DR. WEISS: Yes. Dr. Sugar.

DR. SUGAR: Joel Sugar. Another question that comes up: the indications were never clear to me. That is many patients who had pseudoexfoliation. All patients supposedly had

cataract. Yet, in the submission--again, this data was not reviewed by Roger--about 44 percent I think in the core group had an acuity of 20/40 or better preoperatively. Could that be explained to me?

DR. STEINERT: I was troubled by that as well, Joel. This is Roger Steinert again. And I haven't had the ability to extract all the information on all those patients, but I understood that a lot of those patients were, in fact, patients implanted by Dr. Fine, so I specifically got information from Dr. Fine. So that represents a subset to be sure.

Almost all of those patients who were 20/40 or better had significant glare problems and documented glare acuities in the 20/60 to 20/80 range generally. To the best of my knowledge, there was one that was used in the course of an IOL exchange, and I think there were one or two used in the course of a clear lensectomy for high myopia where the zonules were then judged to be suboptimal.

But I think the vast, vast majority were patients who had glare decrement in their acuity and did have cataracts.

DR. SUGAR: Can I follow up on that?

DR. WEISS: Yes, Dr. Sugar.

DR. SUGAR: So the indications were not just indications listed in the submission? That is some patients had clear lens extraction for myopia in this study?

DR. STEINERT: Apparently a few were put in in patients who had clear lensectomy. That's right.

DR. SUGAR: As you know, and I assume as you experience as well, that makes it difficult to assess when we're not given all the information on the indications for the study.

DR. WEISS: I would remind if everyone can identify themselves before speaking into the microphone.

MR. WELCH: My name is Hillard Welch again. I'm usually referred to as Hid, so I'm going to give it to you that way each time. It will simplify things.

DR. SUGAR: Hid often is used to mean hidden.

MR. WELCH: Beg your pardon?

DR. SUGAR: I'm sorry.

[Laughter.]

MR. WELCH: I missed that. The question

again had to do with the indications that were recorded at the pre-op.

DR. SUGAR: The indications for entry into the study to the best of my understanding of the original submission did not include myopia with clear lens.

MR. WELCH: That's correct.

DR. SUGAR: But Dr. Steinert just told us that some of the patients had this.

MR. WELCH: This was a notation made by Dr. Fine on a couple of the patients. He had other inclusion criteria that he used in enrolling those particular patients. In the reference that Dr. Steinert made to the review, there were 70 percent of those patients exhibited an incidence of glare and an inability to drive, an inability to read small print. These were some of the additional qualifications that Dr. Fine used in evaluating the patient for inclusion.

DR. WEISS: Alice.

DR. MATOBA: Alice Matoba. My question also is in regard to the inclusion criteria. Presence of cataract is one of the inclusion criteria listed, and in Volume II, page nine, the sponsor states that the presence of cataract alone

could be an inclusion alone, that alone. If that's true, I wonder how many patients were entered into the study for that criterion alone and how you can then say that these were all patients at risk, at high risk?

MR. WELCH: I'm not sure I understood the question. You want to know how many were--if cataract alone was an inclusion criteria, how many were--

DR. MATOBA: Cataract alone is--presence of cataract is listed as one of the inclusion criteria.

MR. WELCH: Yes.

DR. MATOBA: And the sponsor has stated that that could stand alone as an inclusion criterion to enter someone into the study. If that is true, I wonder how many patients were entered with just that inclusion criterion and if so how can you state that these patients were all at high risk?

MR. WELCH: I don't think I can give you--my name is Hid Welch--and I don't think I can give you a specific answer to that in terms of numbers, but, yes, cataract was listed in the manner in which it was in the original protocol.

I understand the question is concerning did anybody get enrolled just because of a cataract really? That's a different interpretation, and the answer to that would be no. And I'd have to go back in order to provide you with the specifics as to what was the other inclusion criteria for that particular patient. That is all in the database.

I can't pull numbers out for you right now to say that there were so many that had this, that, or the other thing, but the--yes. To the best of my knowledge of reviewing the cases, there are no instances of a single criteria for inclusion.

DR. BRADLEY: This is Arthur Bradley. Just for clarification, then, is that an error then in the report?

MR. WELCH: I beg your pardon?

DR. BRADLEY: Just following up on Alice Matoba's question, is that an error then in the report, because the report does state--I saw it myself--that cataract alone is an inclusion criteria.

MR. WELCH: It does?

DR. STEINERT: Can you refer us to exactly what you're looking at?

DR. MATOBA: Well, let's see. Volume II,

page nine of 22.

MR. WELCH: Page one of which?

DR. STEINERT: I'm sorry. Dr. Matoba, could you give us that number again?

DR. MATOBA: Page nine of 22 on Volume II is what I've written down, Exhibit 8.

DR. STEINERT: You say nine of 22?

DR. BRADLEY: Page nine.

DR. STEINERT: Page nine on Volume II.

DR. MATOBA: Yes. Exhibit 8.

MR. WELCH: And that may be an error. It is true that that is what I put in the initial response, and I would have to admit that that's probably an error because I don't think that is correct. I believe there was always an additional condition even though it does state--thank you--it does state that cataract is a single inclusion criteria.

But my memory is that that is not a correct final interpretation. Hold on. I'll look for that.

DR. WEISS: I think Dr. McMahon had a comment.

DR. McMAHON: Tim McMahon. My understanding from the submission is that there

were 40 patients that had two eyes in implanted rings; is that correct?

MR. WELCH: What was that again?

DR. McMAHON: My understanding from the submission, that there were 40 patients that had two eyes where rings were implanted? Right and left. Is that correct?

DR. STEINERT: Yeah, there bilateral implants.

MR. WELCH: Yes.

DR. STEINERT: Yes, there were patients who were bilaterally implanted.

DR. McMAHON: And that protocol was agreed to by the FDA to do second eye in an investigative device?

MR. WELCH: It was never so stated as a separate condition, no. No. At no time, though, there was recognition on the part that there were bilateral implants.

DR. WEISS: Dr. Grimmett.

DR. GRIMMETT: Michael Grimmett. I have just two questions at this time. Number one, regarding one of your slides, Roger, that you had up regarding best corrected visual acuity loss. In looking at the Phase II core and Phase II

independent, just roughly eyeballing, adding up the percentages of best corrected loss, worse than 20/40, looks like they're adding up Phase II core is 15 to 17 percent or something like that.

In other area of the study, best corrected visual acuity loss, worse then 20/40 was up near 40 percent in one of the data tabulations. So your slide looks like it's missing 20 to 23 percent or something of the causes. Do the rest of those best corrected visual acuity loss remain under-determined?

DR. STEINERT: Those, no. To the best of my knowledge, what I presented to you was supposed to be the total number. So I don't know. What is the table that shows 40 percent being worse than 20/40? Can you direct us to that?

DR. GRIMMETT: I'll look it up. There were so many different tables in the submission.

DR. STEINERT: I know.

DR. GRIMMETT: That I got confused. So I'll look that up. My second question is a procedural one. In Volume I, Tab Exhibit C, page two, under the Operative Methodology, it states that the intercapsular ring would be implanted just after tearing of the capsular rexis. This

insertion would be prior to the hydra dissection, hydra delineation and phakomulsification.

The video that you showed which I think showed phakomulsification of the lens, removal of the entire crystalline lens, and then implantation of the ring, how would one insert the ring before hydro dissection and hydro delineation? How is that possible?

DR. STEINERT: Before hydro dissection and hydro delineation?

DR. GRIMMETT: Yeah, because that's what it says in Volume I.

DR. STEINERT: Yeah. Well, first of all, that video segment is not from any of the investigators. That actually was from Germany just because we could get our hands on it quickly.

DR. GRIMMETT: Okay.

DR. STEINERT: But that aside, from practical point of view, I know what really went on, and what went on is that as we got experience with the ring, it becomes apparent that the later you can put it in in the case, the easier your life is.

In some cases of extreme laxity of zonules, you're lucky to get through the capsular

rexis, and you want, you need stability immediately.

So the very next thing done is the implantation of the ring. The ring will because of its forces, will basically act like a hydra dissector. It will find the equator just because of its outward pressure. So you can insert it under the anterior capsule prior to hydra dissection, and it will nevertheless end up out at the equator.

However, given my choice as a surgeon, I always deferred it as long as I could, and sometimes I'd be part way through the phako, and then say, well, this is clearly starting to unzipper on me; I need to put it in. But because it does tend, it has the potential for trapping some cortex between the ring and the equator, and then making cortical stripping more difficult, it is desirable to defer the implantation as far into the case as possible.

DR. GRIMMETT: Thank you.

DR. WEISS: Dr. Rosenthal and then Dr. Matoba.

DR. ROSENTHAL: Thank you. Ralph Rosenthal. I just wanted to clarify to Dr. McMahon

that usually at the beginning of an IDE, we agree to monocular implantation or monocular treatment, and then as we become more comfortable with the device and its performance, we will allow the sponsor to move into bilateral implantation or bilateral treatment.

So this IDE has gone on for five years, and so over that five year period, we certainly-- I'm not sure at what point in the five year period, we agreed to the second eye as being implanted, but we had confidence based on the annual reports from the sponsor that there were no problems with the device.

DR. McMAHON: Thank you for clarifying that.

DR. WEISS: Dr. Matoba.

DR. MATOBA: Alice Matoba. I have two questions. First, in your protocol, you specify the range of dates at which the follow-up visits should have to occur. Did you specify when the patients had to be dilated post-op?

MR. WELCH: No. Hid Welch. The answer is no, we didn't specify dilation in the protocol at any specific period.

DR. MATOBA: Then it seems to me that in

undilated people, it would be very difficult to see the lens decentration, especially if it were a small amount, and so I wanted to know how you could have any confidence in your data that long-term stability or that the decentration rate was very low during the follow-up period.

MR. WELCH: You mean without a requirement of dilation?

DR. MATOBA: Uh-huh. Without knowing whether the patients were dilated or not during the follow-up period.

MR. WELCH: We may have made an inaccurate assumption, but there are a few instances in case reports where the examination is noted as not dilated. And thus, the inference is that the others were under dilation at the time of the report.

We did not, and the protocol doesn't specify, that there be dilation at every exam. But just with the way the original protocol--I did not write the original protocol, and I think maybe that should be explained. I barely got on this train after it had left the station. And I picked it up and ran it.

As a consequence, there may have been some

things I should have stopped and gone back and redone in order such as you're asking now to be more definitive, but they were not done, and we continued on the track as it had originally been established, and thus there was no requirement for dilation or no stipulation within the protocol.

DR. STEINERT: This is Roger Steinert. Dr. Matoba, first of all, I totally agree with you that in retrospect that would have been a good thing to specify because it would have improved the ability to see what was going on.

The clinical reality, as I tried to indicate, is we all know, that many of these patients won't dilate beyond if you're lucky five or six millimeters, and so even then we're not going to pick up all levels of decentration, and furthermore we have no decent truly scientific way of even measuring decentration anyway on a clinical basis in clinical practice.

So this is a deficiency. There is no question about it. I think that the minimum statement that you can make is that there was no decentration large enough to become a clinical issue or a clinical problem. That's about all you can say.

DR. MATOBA: My second question is in terms of long-term stability, is there any evidence to indicate that the presence of the ring will stabilize the zonules long term? Many of these patients have conditions in which they're really progressive weakening of zonules over time, and so after many years might not the IOL, the whole thing, just become destablized?

Dr. Witschel, I think, had one case where IOL and the ring became subluxed after six years.

DR. STEINERT: This is Roger Steinert again. There is no question that pseudoexfoliation in particular and possibly some of the other conditions are associated with progressive ongoing degeneration of zonular integrity over time.

And I think all of us who do cataract surgery are seeing patients coming in, sometimes years, even decades, after PC IOL implantation who have lenses that are shifting, dehissing, even falling back into the vitreous against the retina, and that is an issue which we're all going to have to deal with clinically for some time to come.

Whether or not the ring can affect that rate is unknown and a study to prove that would probably start to approach and end off the Midas

study in terms of difficulty in terms of number of patients enrolled, not to mention the complexity of a five to ten year follow-up.

For that reason, I feel that it is inappropriate to make any claim that this ring enhances long-term stability of the capsular bag process. We simply don't have data to support such a claim.

On the other hand, logically, and on a clinical basis, I also cannot conceive that this ring would in any way accelerate decentration, and if you--understanding how it does take tension off of the zonules and get some recruitment from adjacent zonules mechanically, logically one would think it would slow down that degenerative process, but it's certainly not going to stop it.

DR. MATOBA: My concern is just that having the lens might, as a crutch, might encourage the implantation of IOLs in some patients who they should not be implanted whether or not they were agreed to help stabilize the IOL.

DR. STEINERT: Gee whiz. I mean how can you legislate being smart? You know it's a judgment question, and there will be errors in judgment, and I agree with you. But I don't think

--certainly--and that's part of why I wanted to show those numbers of worldwide sales. There is no evidence that this thing has become, you know, everybody's favorite play thing and gets implanted willy-nilly in every single lens case or anything close to it.

It slows you down. It adds cost to the case, and it adds surgical time. So I think there are some significant natural barriers to inappropriate use of the ring.

DR. WEISS: We have Dr. Grimmett, Dr. Van Meter, and then Dr. Smith.

DR. GRIMMETT: Mike Grimmett. Just in follow-up to my best corrected visual acuity statement to Dr. Steinert. The numbers I was quoting of the 40 percent worse than 20/40 best corrected vision actually came from Dr. Lepri's review, page 15, his amended review, as where he tabulated the numbers again. It doesn't, I don't think, agree with the summary slide you had out. There's about half of the patients apparently missing if these numbers are correct.

DR. STEINERT: Okay. Certainly--this is Roger Steinert--as I said, the numbers I presented were the numbers I got from Mr. Welch. If there

are tables that disagree, they should be reconciled and explained. Absolutely.

DR. GRIMMETT: An additional question I had, I didn't locate a physician information booklet typical of other PMAs, and I was just curious regarding the three ring sizes, how does one clinically go about measuring the appropriate width of a capsule diameter to pick the appropriate ring size? Just as a clinician, how do you do that?

DR. STEINERT: Good question. Really there are three ring sizes. What has tended to evolve is I think the majority of people use the average ring because that is an issue. It is not measurable. The one suspicion many people have is that high myops or perhaps extremely advanced large cataracts may have larger bags. So one of the ring sizes is a larger diameter.

The reason that is not used routinely on all is that then it is too big for the average capsule, and I think, although it can be inserted, it makes life more difficult. So I think most surgeons have gravitated toward a strategy of using the middle sized ring, you know, the Mama bear, the Papa bear, and the Baby bear, and they go for the

middle to the one that's just right. And in the vast majority of cases, that works.

DR. GRIMMETT: Mike Grimmett again, just as a final comment. If in general use, I think it would be beneficial for the sponsor to have some type of comments to guide the average practicing ophthalmologist as to how to select the ring size or something of that nature.

MR. WELCH: Hid Welch responding to that. I've noted in my response to the FDA, which they will receive, that we will look at collecting such information and publishing it. Unfortunately, it's of little value in the package insert. It's got to be done educationally on a broad basis because otherwise you get to the point of insertion and you open the package and it is too late.

You're not going to get the information you need at that point for any size determination. So we will look at how we can collect such information and publish it.

DR. STEINERT: Well, certainly I think--this is Roger Steinert again--that the manufacturer should do that, and all of us--in fact, there is an intention among the investigators to publish not only the data but a surgical procedure and what

we've learned along the way in terms of guidance as a separate document in the peer review literature.

However, to the extent that the FDA wishes some guidelines in the package insert, I would be pleased to get that far as to be working with them on that. We can do that.

DR. WEISS: Dr. Rosenthal.

DR. ROSENTHAL: Yeah. Let me address two issues that the panel has raised. The first has to do with package insert or labeling, and certainly we would appreciate whatever recommendations the panel would have concerning the labeling of the device.

The second issue had to do with inappropriate implantation. As you know--or inappropriate use--we would appreciate from the panel some idea as to when it would be most appropriate to implant and when it would be contraindicated, and you might want to choose a percentage of zonular abnormality or something in which the labeling would then state that this was the appropriate time to use it.

But, of course, as you well know, the practice of medicine kicks in. Once a device is approved and a physician has the opportunity and

the right to use any approved device as they so see fit. But certainly labeling and making a statement about contraindications, precautions and so forth, would be appropriate if you felt that that was the thing to do.

DR. STEINERT: This is Roger Steinert. If I could expand on that. You're totally right, Dr. Rosenthal, and I know from talking to other surgeons as well as my own experience that there is almost an inevitable tendency to underestimate the amount of zonule loss in trauma cases. No matter what you think you see pre-op, it will be worse once you get in there.

So, some cautionary statements about not getting overly enthused and also not confusing this ring with something that makes zonules grow back is very, very important. There is a point where there just aren't enough zonules, and I still work closely with my vitreal retinal colleagues to do planned pars plana lensectomies and sutured PC lenses in some of the cases that are referred to me for the ring, because they just don't have enough zonules.

DR. WEISS: Dr. Rosenthal.

DR. ROSENTHAL: Rosenthal. I think, you

know, you've made a correct point, Dr. Steinert, and that is there is enough option to this ring. I'm not a cataract surgeon, but I think it is a complex option, a pars plana vitrectomy and a suturing of the lens implant. But there certainly is another option, and that also would have to be spelled out in the labeling so that the physician would have some idea as to the appropriate time at which the device would be used.

DR. WEISS: Jayne Weiss. Roger, what percentage of zonules absent are the max that you would try to implant the ring in your own practice?

DR. STEINERT: Personally, if I feel that there are more than three to four clock hours of totally absent zonules, I wouldn't go with this ring.

Now you are probably all aware there is a modification that Dr. Robert Cionni came up with that involves a little loop to attach a piece of suture to, and that can then hold the ring in one direction. This is not the subject of this PMA application. That will be an issue for a supplemental application later.

So that ring is not under discussion here, but there is that coming down the pipeline. So

that expands potentially the range. But for the device we're talking about today, I would say three to four clock hours of complete absence. The bigger challenge are these people who have partial absence, because you never really know what else is going on elsewhere. Now are the rest of the zonules nice and strong and happy, or are they all damaged from this injury? It's just that they're more damaged in one area. And that's the kind of a thing that you don't discover until you get into the case.

DR. WEISS: I'm going to have Dr. Van Meter, Dr. Smith, and then Dr. Ho and then Dr. Coleman.

DR. VAN METER: Thank you. I was a primary reviewer for this, and I'd like your reaction to the fact that I feel insulted to have to review data that is as abysmal as this is. There are roving denominators that change. By your own admission, these are patients that are in a referral practice, and it's very difficult to get them back in for examination, which is not the kind of study patients that you want to have.

The company has sold 12 to 16,000 of these annually, and the comment was made that they don't

know how many were implanted, and there are some gaping holes in this. It's almost an affront to us to have to deal with this data and make some meaningful conclusions on them.

Would you please clarify these issues? Dr. Grimmett asked when do you put the ring in. The protocol that we have says the ring is implanted after capsulotomy. Is that incorrect?

DR. STEINERT: Yes. The reality is that this protocol was written a long time ago, five or six years ago, by neither of us at this table, and that is what became the subject of the study. As surgical experience evolved, it was discovered that's just not a smart thing to do.

DR. VAN METER: All right. So that's not the case.

DR. STEINERT: That's the earliest it would be implanted, but not necessarily at that point. That's correct.

DR. VAN METER: Okay. One of your slides showed that 100 percent of these patients would likely go on to vitrectomy if they didn't have the ring implanted. The leading indication was for pseudoexfoliation, and many patients with pseudoexfoliation can successfully have a cataract

extraction with a lens implant and do well.

Can you put these two pieces together?

DR. STEINERT: Yes. The real question is what is the surgeon's judgment? Now, all I can tell you is that we can't go into the operating room and pass judgment on every single case at that time.

The intention and the discussion among the investigators was that it would be cases of pseudoexfoliation when there was evidence of laxity of the zonules which sometimes becomes obvious right away when you start your capsulotomy. Sometimes it becomes obvious further into the case.

Not for the routine use in a patient just because of the presence of pseudoexfoliation material on the anterior lens capsule. So now whether that was complied with, I have no ability to tell you. I don't know.

DR. VAN METER: All right. One other question. There were 25 patients that had 20/20 preoperative vision admitted into the study, and Mr. Welch stated that 70 percent of the patients that presumably Dr. Garbow did had preoperative glare, means 30 percent of them do not have preoperative glare.

So if you've got 25 patients that probably didn't have any preoperative glare symptoms, were these done for high myopia? Or do we have any way of knowing? I mean is this--

MR. WELCH: Hid Welch. Not that I'm aware of. I don't remember any statistic or data that would show that or that recorded that. There are indications given on the report that we asked Dr. Fine to provide, and they range from all kinds of things, not just glare.

And most, some of them even called it off for quality of life because the patient was continuously complaining of the inability to do whatever it was they wanted to do in their daily life. And these were listed as part of the--

DR. VAN METER: Okay. But since this was a device that is used in complicated patients that have a higher than usual risk factor, why are we operating on 20/20 patients with no glare in a procedure that has a higher than usual risk criteria?

DR. STEINERT: First of all--this is Roger Steinert--I understand your question and I agree. I had the same reaction this past month when I came across these data. And I did not personally use

any of these implants under those circumstances.

Since we didn't have the ability to track down every one of those, as I said earlier, we did ask Dr. Fine, who seemed to have done a large number of those, to give an accounting. I'm not sure about the 70 percent number. I haven't done that calculation. Mr. Welch--

DR. VAN METER: That came from Mr. Welch.

DR. STEINERT: Yes. This said, but my recollection is that Dr. Fine did use this on one or two, and I don't think there were more than that, high myops who are undergoing clear lensectomy for refractive surgical reasons.

DR. VAN METER: Okay.

DR. STEINERT: And I believe there was one that was an IOL exchange where the capsule seemed to be unstable after the original implant was out.

All the rest, they either documented glare or there were these functional complaints that suggested glare and night vision issues, et cetera, et cetera. But they might have 20/20 or 20/25 high contrast acuity.

DR. VAN METER: Okay. Thank you. I have another question that I'd like for ya'll to answer if you can. If you envision this round plate as

being the lens capsule complex and when you put the ring inside it, it stabilizes it and makes, you know, a round device that supposedly uses all of the zonular fibers for stability.

But if you're missing three clock hours, say from 11 o'clock to eight o'clock, of stability, and you have a lens implant and the ring in place, most of the tension of, you know, mobility to the eye is going to be on the 11 o'clock fibers and the eight o'clock fibers. And actually by missing three clock hours, you're going to have increased pressure on those that are on the edge of the gap, if you will.

And do you all have any studies to show that this is stable long term? Two years is really not long enough to show what's going to happen. I mean my fear is that this diaphragm is going to tear the 11 o'clock and the eight o'clock fibers and then you have four clock hours of instability from 11:30 to 7:30.

And from the data that you have, this is really not anything that's going to show up in a year or two.

DR. STEINERT: Well, first of all, I agree with you about any claim about long-term stability.

I don't think we have data that can substantiate such an indication, and that's why that is not being asked for.

From a mechanistic point of view, I'm not aware of any sophisticated biomechanical studies one way or the other. From a kind of naive conceptual point of view, I think that you're right, that the zonules on the edge of the total defect are going to be the ones under the most pressure.

The concept is that in the presence of the ring, though, that at least those--let's say your 11 o'clock zonule is getting a little help from the guy at 12:30, which is getting a little help from the one at 12. In the absence of the ring, that's not happening. So it ought to be making the best of a bad situation.

DR. VAN METER: Okay. I have one more question, and thank you for taking the time to answer some of these questions that were not necessarily of your doing. But since you're the one that we have to direct these to, forgive my frustration.

The number of explantations came from surgeons that put the ring in, and then thought

maybe it would be better not to have a ring in. And it shows that the difficulty of preoperative evaluation of zonular stability is one of the main problems that surgeons would have in having this device on hand.

Do you have any feel for how many patients were designed to get the device from preoperative planning versus what percentage had the device implanted when the surgeon determined intraoperatively that the ring would be helpful?

MR. WELCH: Hid Welch. The answer to that is no, I don't have that information for you here, but there are several instances in the case reports of the decision being made intraoperatively to use the ring.

DR. VAN METER: Right.

MR. WELCH: And we can segregate those from the database to then evaluate it.

DR. VAN METER: Well, I was really asking Dr. Steinert as a practicing cataract surgeon that if he had a feel that, you know, 20 percent of them you decide intraoperatively, ten percent or 50 percent? I just--

DR. STEINERT: Oh--

DR. VAN METER: I don't use the ring so I

don't know practically how it shakes down.

DR. STEINERT: Yeah. Offhand, I can only think of a cases, Woody, where I truly didn't anticipate anything until I got into surgery. Every once in awhile, you know, there are ones where the patient dilates so much better at surgery, and all of a sudden you say, whoa, I can see the edge of that. I didn't expect that.

And then even that, I wouldn't necessarily put a ring in, but then you start manipulating and everything starts moving and you get surprised. But that's a real minority. What you're alluding to, though, and I think is a bigger subgroup, is the pseudoexfoliation group. That's the one where you're must likely to not know going in whether you need it. So what I do is I consent all of my pseudoexfoliation patients in advance and tell them that I want to be able to use this if they need it, but I will only use it if they need it. It ends up being about five percent probably of the pseudoexfoliations.

DR. VAN METER: So, by and large, you would order this ring for patients ahead of time?

DR. STEINERT: Yeah, we have--since it's not like an implant with power and everything, it's

easy to have a stockpile, so you just have a couple lying around.

DR. VAN METER: Okay. Thank you.

DR. SUGAR: Can I comment on that issue?

DR. WEISS: Yeah, I'd prefer to keep discussion of this particular matter to be placed later on in the game, and then now do you have a particular question on this?

DR. SUGAR: Well, just that in Mr. Welch's data they presented to us, they listed 133 patients having the decision made intraoperatively in the independent Phase II.

MR. WELCH: Would you repeat that, please, sir?

DR. SUGAR: In your data that you presented to us--

MR. WELCH: Yeah.

DR. SUGAR: --there were 133 patients listed as having the decision made intraoperatively. I was going to ask the same question of how were they consented if the decision was not made until the time of the operation?

DR. WEISS: Thank you.

MR. WELCH: What table is that to which you're referring, sir?

DR. SUGAR: I will try to retrieve it.

DR. STEINERT: Quite frankly, Joel, part of that answer, I'm sure, relates to the difference between the independent investigator group and the core investigator group and how they approach the study and why they were asking for the ring.

DR. WEISS: While we're looking into that, Dr. Rosenthal had a comment.

DR. ROSENTHAL: With regard to Dr. Van Meter's comment about greater than two years, this device has been under investigation since 1996.

MS. THORNTON: Would you speak into the microphone, Dr. Rosenthal?

DR. ROSENTHAL: The device has been under investigation since 1996, so I think there's probably a lot of patients who were enrolled longer than two years.

The other thing is as Dr. Steinert noted on his slide, from the years 1992 to 1996, there were several thousand that have been implanted worldwide, and I would hope that we would have a recommendation from the panel regarding this issue of long term.

DR. VAN METER: Woody Van Meter. Weren't those devices sold?

DR. ROSENTHAL: Oh, sold, sorry. Yes. Well--

DR. HO: Allen Ho. Furthermore--

DR. WEISS: I think Dr. Smith was first, then Dr. Ho, and then Dr. Coleman. We're going to try to go back to the original.

DR. SMITH: Janine Smith. In Volume I, Exhibit C, there is a protocol evaluation listed and a dilated fundus exam is specified in the evaluation process. Do we know that those were performed at least on a certain interval in all of the patients since somebody asked previously how could you determine if there was IOL decentration if you're not certain that the patient was dilated? Are we certain that every patient post-operatively had a dilated fundus exam because there is no place on the data report form to document that?

DR. STEINERT: And that's exactly right. It was not called out as a specification. So we have no way of certifying that.

DR. SMITH: But it was specified in the protocol that it would be done, on Exhibit C.

DR. STEINERT: Which page are we talking?

DR. SMITH: Page two of three.

DR. STEINERT: Yeah, that's the page I'm

on.

DR. SMITH: Second paragraph at the top under Evaluation, it describes the evaluations to be performed and dilating fundus exam is listed there.

DR. STEINERT: Depending on how you read that, it might be interpreted as just a pre-op dilated fundus exam, I believe. It's ambiguous. It's not great wording.

DR. SMITH: Perhaps that referred--well, I don't think that can refer to just preoperative, because later on in the sentence, well, there's a semi-colon there, and then there is intraoperative complications. So maybe that is a pre-op evaluation. It was only specified to be performed preoperatively.

DR. STEINERT: Really, it's ambiguous.

DR. SMITH: The second question is on Exhibit 2 in Volume II which is a data report form. Under the Pathology and Complications, it lists inflammatory deposits on the IOL and fibrin in the pupil as complications. And Dr. Steinert, on your slide for documenting the rate of inflammation post-operatively, you listed 1.2 percent. Were these the criteria used to determine a diagnosis of

iritis, because that's very low, and it states that this time period was one week to closure, and one week after surgery in a complicated case like this, it wouldn't be unusual to have an anterior segment reaction. So I'm wondering if it was just inflammatory deposits on the IOL and fibrin used to define iritis?

DR. STEINERT: It, first of all, I should clarify. The acute post-op phenomenon was discounted because that's essentially 100 percent iritis on the first day.

So this would be beginning at the--I'm pretty sure--we did this at ten to 14 weeks.

DR. SMITH: So there was a specific--Janine Smith--there was a specific time point for iritis to be evaluated?

DR. STEINERT: It was a report that--yes, it was part of the post-op report, but that number, to the best of my knowledge, was generated by people specifying there was iritis. They used that word in the post-op report so the presence of a precipitate on an IOL in the absence of anterior chamber reaction would not have been called out as iritis.

DR. SMITH: So then since it's not listed

as already on the form, they would have checked under "Other" and written iritis?

DR. STEINERT: Yes.

DR. SMITH: One other question about the method of insertion. In the video, you showed a forceps being used to insert the ring, but you commented that you personally used an injector. Do we have any information on which procedures were used by surgeons in this study?

MR. WELCH: Hid Welch. The answer to that is that we do partially because what happened was in the early stages of the study, the doctors found that there was an injector on the market. Then an injector was requested by the Morcher Company from another manufacturer.

At that point, we also got a notice from the FDA that the injector was not approved. So we submitted a 510(k) for the injector, which was subsequently approved, and a restriction on that 510(k) stipulated that it could be used by the investigators only. It was not to be used for any other surgeon for obvious reasons.

The core group, to the best of my knowledge, does have the injector, and once it was approved, they have used it, but they did not note

it on the form. We do have a number of case reports where it was noted that an injector was used. We have indications of the benefit of the use of that injector on those case reports, but that's all.

DR. WEISS: In the interest of time--Roger, sorry. You had a comment?

DR. STEINERT: I was--just to clarify, Dr. Smith, that I've done it both ways, and I can just tell you from personal experience, it is a little easier and a little faster to use the injector in my personal opinion, but I have done it the other way, and I have not encountered any adverse issues. It's not that you break the ring or puncture the capsule. It's just a little--you have to do a hand over hand maneuver. So it's just a little bit more complicated.

I also know Dr. Witschel doesn't like the injector. So there's a range of opinion as in many surgical things.

DR. WEISS: In the interest of time, we are going to have another question by Dr. Ho and then followed by Dr. Coleman, and then we will move on to the FDA presentation.

DR. SUGAR: Could I add the documentation

for my comment earlier?

DR. WEISS: Yes.

DR. SUGAR: In Volume II, Exhibit F-2 revised, there are listed for Phase II independent 133 intraoperative zonular dehiscences. In Phase II core or phase I, there were no intraoperative dehiscences listed. I don't know how to interpret that, but the only way that I could interpret it was that these were recognized at the time of surgery and not preoperatively, because none of the other ones were listed that way.

DR. WEISS: While you're looking at that, maybe Dr. Ho could ask, proceed with his question.

DR. HO: Allen Ho. Just a question for Dr. Rosenthal, first of all. The comment was made regarding long-term stability and you had suggested that because this had been implanted for so many years, that there might be some information available to us.

I'm not aware of long-term stability information, unless I'm mistaken. Did I miss something?

DR. WEISS: I would just remind you the sponsor is not looking for approval for long term.

DR. HO: Okay.

DR. WEISS: So I don't really think we need to discuss that issue. I think it's been suitably handled.

DR. HO: Nor am I comfortable making a comment about that with that data. So that's my first comment.

The second comment is that, you know, our charge here is to advise the FDA based on data, and one of the principles of a good study design is to identify, first of all, the patients with whom--in whom you're studying so you can make relevant recommendations to those patients based on the results of the study.

It seems to me that the core group is the group of patients that might have the best follow-up, the best accountability, but I'm still at a loss in defining who those patients are. And I'll give you a for example.

If you turn to Volume I, Exhibit F, as a retina surgeon on this panel, for example, I am struck by the relative low rate of retinal detachment post-operatively that was not present preoperatively, the relative low rate of CME, and if those methods of ascertainment are valid and reliable, then I think that's great.

But I can't comment to what patients they apply. For example, if you go to this Exhibit Chart 1 on the Phase I core group, I see a listing of the diagnoses on the far left side. But if you look at the Y axis, it's defined as number of patients/eyes. And that's confusing to me, because some of the patients had more than one eye implanted. So I need to identify what the study group is a little bit better before I can make comments.

DR. WEISS: We're going to have questions by Dr. Coleman next and then we'll move on to the FDA presentation.

DR. COLEMAN: Dr. Coleman. Did you want to respond?

MR. WELCH: No, go ahead.

DR. COLEMAN: My question is do you have those numbers of subjects or eyes that had preexisting glaucoma prior to entering the study? Since, as in the core group, about 39 of those 75 eyes had pseudoexfoliation, you would expect there to be a high incidence of preexisting glaucoma.

And it's important because it appears that the majority of the elevated intraocular pressures after surgery were on those with preexisting

glaucoma. So it's nice to have also the denominator of the eyes that started out with preexisting glaucoma.

DR. HO: Jayne, can I comment?

DR. WEISS: Yes, briefly.

DR. HO: It's relevant to this because it again identifies that you need to clarify who those patients are. They may have cataract and pseudoexfoliation. Some of the patients, in fact, if you look at the table in the core group, are not expected to have cataracts here, because the number is about 75 percent. So I'm a little bit concerned on commenting when I don't know exactly whose those patients are.

MR. WELCH: Understand. Hid Welch. I'm looking at Exhibit F-1b, which is I believe the table you were looking at, the chart; is that correct?

DR. HO: Right. You described--Allen Ho--you describe it as the etiology table. So I'm looking for trying to identify your study population here.

MR. WELCH: Yeah.

DR. HO: It's not clear to me.

MR. WELCH: And F-1b is simply a--

DR. STEINERT: Are you talking about F-1b?

DR. HO: F-1b.

MR. WELCH: He's looking at this.

DR. STEINERT: The chart, F-1b, or are you looking at the table F-1a?

DR. HO: 1a.

DR. STEINERT: Yeah, okay.

MR. WELCH: He's looking at 1a.

DR. STEINERT: And I'm sorry. I'm still not exactly following the question. What is--

DR. COLEMAN: This is Dr. Coleman. My question was is just in terms of the number of preexisting cases of glaucoma.

MR. WELCH: Right.

DR. STEINERT: But what is--

DR. COLEMAN: Why? Because in terms of the patients that had elevated intraocular pressures that required treatment, that was one of your points and variables that you were following afterwards. The majority of those individuals were said to have preexisting glaucoma. And so it's also nice to know how many preexisting glaucoma individuals in the study didn't have elevated intraocular pressures afterwards.

DR. STEINERT: In other words, did the

ring somehow reduce their intraocular pressure? Is that the question?

DR. COLEMAN: No, it just gives you kind of a denominator whether you know exactly what's going on because if only 20 individuals in the study had preexisting glaucoma prior to implantation of the intraocular lens and the ring, and 20 had problems with intraocular pressure after the surgery, that's a little higher than you usually see. And so it gives you some idea of exactly what the population is.

It might be that 30 people or 20 people had preexisting glaucoma, and you only had trouble with ten of them with intraocular pressure afterwards which would be expected in a population like this. That's the main thing because it just gives you a denominator to work with.

DR. STEINERT: The purpose--to be sure that's an interesting question. I think, you know, from our point of view, the point of that table was simply to address the question as to whether there was a safety issue and whether there was any indication that these procedures and the use of this ring in particular caused an undue or alarming or concerning rate of elevated intraocular

pressure, and it appeared that the answer was no. And that's where the analysis stopped.

DR. WEISS: I'd like to thank the sponsor for their presentation, and we're going to have you move back from the table and have the FDA come up and give their presentation. Please.

FDA PRESENTATION

MS. LOCHNER: This is Donna Lochner. I'm going to give some introductory comments to the PMA. The PMA for the Morcher Capsular Tension Ring was received by FDA on October 16, 2001, and was accepted into the Office of Device Evaluation's expedited review program. Expedited review is granted for first-of-a-kind devices for which no approved alternative treatment devices exists, and in the case of the capsular tension ring, which may potentially reduce the risk of morbidity for the indicated patient population.

Expedited review is intended to move applications to the front of FDA's review queue, but does not waive clinical or scientific safety and effectiveness endpoints.

Rather, consideration of the difference in the risk-to-benefit analysis because of the lack of alternatives is addressed in the design of the

clinical study protocol.

The sponsor chose to participate in OED's modular PMA program which allows for review of sections, or module, of the PMA as they are completed. When all information that is required to be included in a PMA application has been submitted, the PMA may be filed and review proceeds.

The final clinical section of this PMA was submitted on October 16 and so this is the filing date of the Morcher PMA.

Three modules preceded the submission of the clinical data and contain the sterilization procedures and validations, the manufacturing and engineering procedures and validations, and the biocompatibility data.

There are outstanding issues in each of these scientific areas. At this time, FDA is awaiting adequate responses from the sponsor. In addition, completion of the bioresearch monitoring inspections and scheduling and completion of the good manufacturing practices inspections are also outstanding.

Today, we are asking the panel to review and make recommendations on the clinical data

contained in the PMA. However, the status of the PMA is provided to make sure that you understand the FDA awaits adequate responses to the remaining scientific sections of the PMA prior to any final decision on the application.

We appreciate the efforts of the panel and particularly the primary panel reviewers, Drs. Sugar and Van Meter, who reviewed the document on a compressed schedule to the expedited status of the PMA.

In balance, we felt it most efficient to proceed with the panel meeting in consideration of the potential benefit of this device to public health.

I'd also like to acknowledge the exceptional efforts of the FDA review team, and particularly Joel Glover, the engineering and lead reviewer, and Dr. Bernard Lepri, the clinical reviewer.

I'd also like to acknowledge Dr. Kesia Alexander who was the lead reviewer for most of the IDE. All three of these individuals have made significant efforts in consulting with the sponsor over the years.

Now, I'd like to introduce the lead

reviewer, Joel Glover, who will present an overview of the scientific non-clinical sections of the PMA.

MR. GLOVER: My name is Joel Glover. As Donna mentioned, I'm the team leader for the application, and as she also mentioned I'd like to acknowledge Kesia Alexander who was the team leader before I became involved with the application.

I'm going to present a brief history of our experience with the PMA. The capsular tension ring PMA was done under our Modular PMA Program. It was actually initiated with a shell outline of the intended modules back in August of 1998, and followed shortly thereafter with the submission of some of the preclinical modules.

The clinical module, if you will, that actually triggered the PMA was received in October of last year. The modular PMA was composed of four modules. Module 1 was general information. Module 2, biocompatibility. Module 3, the microbiology/sterilization module. And Module 4 contained the manufacturing. And again, the PMA was to be the clinical data.

Module 1, general information, contained general information about the device, the applicant, manufacturing sites and FDA considers

that complete.

Module 2 was to address biocompatibility of the device. The device is made of polymethalmethacralate. The sponsor provided cytotoxicity test data and residual levels.

FDA has some outstanding issues with this module, in particular the nature of the specific PMMA material that the sponsor is using to construct their device, and some issues with residual levels and identifying what those residuals are.

The sponsor only performed essentially cytotoxicity testing. So FDA has concern about the lack of biocompatibility testing or having a justification for omitting the testing. The issue has been discussed many times with the sponsor and FDA and the outcome of that is essentially that the sponsor has chosen to use the clinical data from the PMA to demonstrate the biocompatibility of their device as opposed to conducting further tests to support biocompatibility.

And this is an agreement that--I shouldn't say agreement--but this is an argument that FDA is willing to consider for this device.

Module 3 was the microbiology/

sterilization. It contains such things as how the device is sterilized, validations for the sterilization procedure, and a study of the shelf life of the device. There are some outstanding issues with this module as well.

Module 4 is the manufacturing section. Both the Office of Compliance which looks at the good manufacturing practices and quality control procedures and reviews that and conducts the GMP inspection has outstanding issues, as does the Office of Device Evaluation, and these will need to be addressed before an ultimate approval of the PMA.

I would point out that FDA doesn't believe that these outstanding preclinical issues warrant delaying the panel's review of the clinical data for the PMA, and that's why we brought it forward to you at this early stage.

Finally, the PMA was submitted last year and contained the results of the clinical study of the device, and in a moment, Dr. Lepri will present his analysis of the clinical data. And finally, I'd just like to thank the panel for their review and deliberations today and also the members of FDA's review team for their reviews and quick

responses, as well as the sponsor's responses with regard to this expedited PMA.

And if there are no questions, I'll introduce Dr. Bernard Lepri, the clinical reviewer.

DR. WEISS: Dr. Bradley has a question.

DR. BRADLEY: I just wondered if there are any reasons to question the use of using the clinical data to ascertain biocompatibility? You said there was some argument about it. I got the impression that the FDA has some reservations about the validity of that approach. Could you comment on that?

MS. LOCHNER: Well, I think first of all typically biocompatibility testing is done preclinically to screen for potential problems before a material is implanted in the eye.

While we didn't de facto accept the sponsor's argument that this is polymethalmethacralate and so should be allowed in the eye, because we believe the sponsor had to identify what type of polymethalmethacralate was used, we felt that their worldwide experience to date warranted initiation of the IDE study.

It was our understanding at the time that they would then proceed to collect the usual

biocompatibility testing. When you go through the usual battery of tests and look at what would the clinical study not address, you come down to two areas. One is the ocular implant test in rabbits.

Certainly the clinical data would suffice as a replacement for that, but what the ocular implant test does do is look at histopathology that isn't provided in the clinical study. But I think a reasonable argument could be made by the sponsor that their outcomes wouldn't suggest problems. And so not having that histopathology from the rabbit study I think they could make a valid argument for that.

The second area that the particular clinical data does not address is the carcinogenicity testing. And again, we believe the sponsor can make an argument that even though this is a PMMA that has not been used in the U.S. previously, we think they could make a valid argument that there is no reason to expect that this PMMA would be a carcinogen.

So this is where we are today. However, we felt it important that the panel understand that unlike your usual review of clinical data, an additional component is that these clinical data

are being used to support the biocompatibility.

So if there was any question that you might have, not even--you know, any issue with the outcomes that in the past you would have said, oh, this is no problem, at least you're aware that the usual biocompatibility testing was done so that when you say you have no concerns with the outcomes, you know, you're aware that the usual biocompatibility wasn't done.

So we're providing all this background so you understand, you know, what is atypical about this document.

DR. WEISS: Thank you. We're going to go on to Dr. Lepri's presentation.

DR. LEPRI: Thank you. Good morning, members of the panel, sponsors, FDA, staff members, and guests.

I'd like to make some introductory comments, but I have taken the liberty of compiling data and trying to present an overall picture of what was given to us in this PMA, and I apologize for any inaccuracies I may have, but they are limited by the numbers that I was presented with, and as one mentioned, we had a roaming end, but we slowed down the speed of that roaming end with the

first deficiency letter.

At this time, I'd also like to thank my fellow FDA members for their encouragement and support: Dr. Rosenthal; Donna Lochner, the early days with Dr. Kesia Alexander, and especially my own personal "Lord of the Rings" hero, Joel Glover, who has helped keep this entire application and process moving smoothly and accurately and helping me to meet these very compressed time schedules.

Okay. The PMA application presents varying forms of the indications statement, and I'm going to present those to you in the next few slides for your consideration when we later on in this process ask you for your labeling recommendations.

The initial indication in the beginning of the PMA and the IDE read that it is used for the stabilizing the capsular bag in cataract surgery with IOL implantation, in cases of pseudoexfoliation syndrome, where there is subluxation of the lens or zonular damage as in Marfan's syndrome and in traumatic cases, and cases where pars plana vitrectomy has been performed.

Next. The next indication statement is in Exhibit 1, and all the items you see listed there

have been added to the indications statement in this proposed labeling. I want you to particularly note stabilizing the capsular bag in high myopia, stabilizing operating conditions, implantation of foldable IOLs, circular expansion of the capsular bag, and prevention of unilateral shrinkage of capsular bag, and prevention of capsular fibrosis.

The next is in Exhibit K where once again high myopia is missing, is added, and some of the same items are repeated as in Exhibit I, but compressed.

The CTR, the capsular tension ring, is a flexible, one-piece ring of PMMA that ranges from ten to 12 millimeters in diameter. Utilized in this trial were three types: the 14, 14A, and 14C type rings, which differ in dimensions to accommodate the differences in capsular bag sizes of individual eyes.

The study was comprised in this PMA of two phases: the Phase I core and Phase II which included core investigators as well as independent investigators.

And Phase II was conducted primarily to provide confirmatory data. This was a prospective, open label, multi-site/multi-investigator trial.

Demographically, the core group was comprised of 27 males and 48 females. The age stratification was that 24 of those 75 were between the ages of 70 to 79, and 26 of them were either 80 years of age or older.

Phase II combined core and independent investigators was reported as 238 males and 237 females. You may note that those numbers do not add up to the total of 415 patients as noted elsewhere in the PMA. That's another one of those discrepancies.

The demographics of the preoperative pathology show that there were some significant pathologies that were majorly represented in this investigation. There were a combined total of 161 pseudoexfoliation patients, followed most frequently by trauma cases, and as you can see, there are cases, 12 cases of Marfan's and 22 cases of vitrectomy, that were at the time of surgery when they implanted the ring.

Of course, the most widely represented was the pseudoexfoliation. The data results for effectiveness and/or safety were not stratified by preoperative pathology other than for capsular fibrosis and contraction and IOL decentration.

The only data presented on the 98 trauma cases was visual acuity. I also wanted to make note that we have not had any data presented to FDA in the early post-operative periods where we would get a very good indication in the response of these patients to the implantation of the ring, and it has been noted in your deliberations as well as the sponsor's presentation on very low rates of iritis, that those were calculated for the overall period, and out to one year or two years in the case of the core.

Accountability. The accountability, when calculated by FDA's criteria, was higher than that obtained by the sponsor and overall reasonably good. The Office of Device Evaluation recommends a minimum accountability at the time of submission of a PMA to be at least 80 percent. You can see from this chart that Phase I was at 88 percent at one year with three lost to follow-up. And Phase II was at about 81 percent at one year with approximately 63 lost to follow-up.

The endpoints established for this investigation were IOL centration both pre and post YAG as a major effectiveness criterion, and the safety criteria were the FDA IOL grid. These were

safety variables. There were no standardized criteria.

Let me step back. There were no standardized criteria, as mentioned by Dr. Steinert, for measuring IOL centration and there was no establishment of a criterion of what would be considered significant or expected.

The FDA IOL grid was only used as a guide for the sponsor to use in evaluating complication rates of implantation of this device. In no way was it intended for the sponsor to have to meet the criteria established in the FDA IOL grid since this is not an IOL.

IOL centration at one year post-op. This slide presents the number of eyes in each phase as identified by the individual investigators. Phase I core had the highest at ten percent. Auffarth, et al., in 1994, conducted post-mortem studies of eyes with PXE patients and noted a higher incidence of decentration in bag fixated IOLs, this resulting from intraoperative zonulysis.

Intraoperative zonulysis ranges from 13.1 percent to 17.9 percent according to the literature. So we can see the IOL centration measured with the methods used and not firmly

established were well within those ranges postoperatively.

We further analyzed these data to establish how the IOL centration was rate wise even though the end values were small for those individuals who had YAG capsulotomies performed, and we can see that a rate analysis of IOL decentration greater than or equal to one millimeter post-YAG produces results that are comparable to those reported in the literature for the amount of the zonulysis and decentration.

Phase I core had 12 YAGs by the last set of data that I have received, and two of them reported that they had decentration of greater than or equal to one millimeter. And in Phase II, there were seven YAGs performed. One of them reported as having greater than or equal to one millimeter of decentration at a rate of 14.29 percent.

PXE patients who were the bulk of the patients in this investigation often exhibit postop IOL decentration due to intraoperative zonulysis. As I mentioned before, the literature rates of zonulysis in PXE range from 13.1 to 17.9, and the CTR post-YAG decentration rates range from 14.29 to 16.0.

Also, very common in this, these types of cases, are capsular fibrosis and contraction, which were issues that were mentioned in the proposed labeling. Since capsular contraction results from the fibrosis of the capsule, I took the liberty of combining these data and presenting them all on one chart.

The total fibrosis for all phases reported was 9.5 percent and the total amount of contraction reported was 3.2 percent. And the last column, that's correct. There was an error last night when I was preparing for this.

YAG rates. The rate of PCO calculated for core group eyes evaluated at one year is 28 percent. There were 14 out of 50 eyes. I believe it was Exhibit H-1 and H-2 that listed the complications. And at the bottom of that list, it claims that the percentages were based on the number of eyes examined. So for the core group that was 50.

And that's where the 28 percent is from. I transferred the rates of the percentages of YAGs and the percent of fibrosis and capsular contraction on to this chart also. That way you can compare them coming to this review.

39 of the 75 subjects enrolled in Phase I had PXE, and it's reported in the literature by Naumann and many others that PXE patients have higher rates of PCO postoperatively.

The next slide, please. This slide presents the numbers of postop IOP increases in eyes at one year, 11 to 13 months, who did not have preexisting glaucoma. These were reported by the sponsor in Amendment No. 3 of this PMA. They were not classified as adverse events by the sponsor. The sponsor claimed that they were not classified as adverse events because the patient's other conditions were more serious in the investigators' opinions.

The FDA considers all post-op IOP increases as adverse events whether they are device related or not, and you could see the rates that I calculated based on the numbers and the level of accuracy that was presented to me that there were two in the core group, which gives you a rate of four percent, and 14 in the independent group, and at that time point at one year, it's reported in Amendment 3 that 297 patients were evaluated, and that's the denominator that I used to obtain a rate of 4.7 percent.

Visual acuity. While the endocapsular tension ring is not directly responsible for visual acuity outcomes, their analysis is valuable in representing the benefits to the subjects of cataract surgery within the scope of this investigation.

One can see that there were significant numbers of eyes with better than 20/40 BSCVA preoperative. 74 of the 75 core group eyes were reported as having cataracts. The sponsor reports BSCVA of greater than or equal to 20/40 post-op in the core group at a rate of 87.87 percent, which is close to the target value of the FDA IOL grid of 92.5 percent.

Phase II subjects did not fare as well postoperatively with respect to best corrected visual acuity. The sponsor did not provide sufficient detail for the Phase II results such as best case analysis or results stratified by preoperative pathologies to document the cause of the lower than average acuity outcomes postoperatives.

The sponsor reported that there were 12 eyes of 11 subjects in Phase II with macular degeneration, but this in no way accounts for the

percentages of BSCVA reported.

Also, the sponsor did not calculate the rates in this table. I calculated these rates. They did not present this data.

Explants and secondary interventions. I think this is a repetition of Dr. Steinert's slide. There was one secondary reintervention due to capsule/IOL problems a one week.

There were five explants in Phase II subjects' eyes; three were in the core group and two in the independent group.

And there were seven others performed during initial surgery, two of which were due to procedural complications, four due to inadequate capsular/zonular support, and one for an incorrect ring size.

Inflammatory complications. The most noted in these populations would be iritis, synechiae, IOL lens deposits and CME.

The inflammatory complications in this report were these and many others which were not of significant numbers to mention at this time.

Iritis. The sponsor's presentation reported six cases of iritis that are not presented in Amendment No. 3. At the time of their

occurrence is not noted, and the PMA did not report any postoperative data earlier than one year. So we have no information on the critical postoperative, immediate postoperative, time periods.

Pseudoexfoliation patients according to the literature exhibited an impaired blood-aqueous barrier which would yield higher rates of iritis postoperatively which we have not seen any of the data presented in the PMA.

They also have increased fibrinoid reactions which lead to potential posterior synechiae and IOL cell deposits.

There were some synechiae reported in Amendment No. 3 in Exhibits H-1 and H-2, and there were--although the rates were low--okay--and one would expect as well as hope to see these lower rates at one year post-op. As I mentioned before, we didn't see anything early on. The rates were essentially one percent in Phase II and approximately two percent in Phase I, and it was in the nature of anterior synechiae.

Cystoid macular edema. The sponsor's presentation reported--that was forwarded to FDA prior to today--reported 11 cases of CME out of 524

patients, which I later learned that those were 524 implants, not patients, and these 11 cases are not explained with reference to the time point of occurrence, and the rate is not calculated using a denominator of the eyes examined, as it should be, but rather they used a denominator of the total number enrolled and treated. And so we might get more valuable information for purposes of labeling in the performance of this device if we knew this occurred and it was based on the number of patients actually evaluated.

When we compiled--we--I compiled the one year data that was presented in Amendment No. 3, I found two percent rates of CME at one year for Phase I core subjects and all Phase II combined subjects.

Now I will present the questions. Some of the questions I will make some reference to some of the information found in our literature review, just as a matter of background, and I fully acknowledge your expertise and that you may already know this.

Question No. 1: The sponsor has not performed the standard battery of biocompatibility testing on the device, and has proposed to use the

clinical data to document the biocompatibility of the device. Do the adverse events and their rates reported in the PMA support raise any safety concerns from your clinical perspective?

Question No. 2: Patients with high myopia were not included in the U.S. clinical study. Do the data in the PMA support these proposed indications for use?

Question No. 3: Do the clinical data presented in the PMA provide sufficient evidence and effectiveness of the device for the proposed indications for use, taking into account the revisions in response to question number two, if any?

Question No. 4: Do you have any recommendations for revisions or additions to the labeling as proposed by the sponsor? Please consider the following issues in your deliberations:

Part a, high myopia, lens extraction without IOL implementation;

Part b, progressiveness of syndromes such as pseudoexfoliation and Marfan's.

And part c, late onset of dislocation of capsular bag containing IOL and ring in

pseudoexfoliation syndrome.

And I will note that in the literature review, we found Jehan, et al., at 2001, and he presented the results of an eight eye/seven patient study, and these were patients who had previously undergone uncomplicated cataract surgery with IOL implantation. All of them, 100 percent of them, experienced delayed dislocation into posterior chamber.

And the mean time for dislocation was seven years. And there was one other literature report that reported this occurrence as late as 12 years post-op.

And part d, the use of Type 14 rings in pediatric patients, size issues and potential radial tears in capsular bag. And the origin of this concerned is an article published by Dietlien, et al, in the year 2000, of complications in a four-year-old who experienced upward displacement of the bag, capsular bag, after the ring was implanted interoperatively.

They claim in this article that the adult rings were not a good choice for pediatric patients for two main reasons: the proliferation of lens epithelial in a growing eye and the weak zonules.

And these combinations led to CTR dislocation and distortion. And the size of the rings may be too large for some pediatric patients, particularly Marfan patients or trauma victims, and has the potential to cause radial tears of the capsular rexis.

Thank you.

DR. WEISS: Thank you, Dr. Lepri. Now we're going to open the floor for any questions from the panel to Dr. Lepri or the agency.

Panel Questions for FDA

DR. WEISS: Dr. Van Meter.

DR. VAN METER: In your last page of questions, you did not address the efficacy--

MS. THORNTON: Dr. Van Meter, could you speak into the microphone, please?

DR. VAN METER: Yes. Woodford Van Meter. On your questions on 4, part a, b and c, you did not get into the demonstrated efficacy of reducing capsular fibrosis or capsular contraction. Is that still a concern of yours?

DR. LEPRI: That's still a concern. That was presented; it was part of the presentation, and I presented that data. We just had these additional concerns that were obtained from the

literature and that's why they were mentioned separately at the end, and I didn't want to bore you to death with providing you exhaustive literature.

DR. WEISS: Dr. Bradley.

DR. BRADLEY: Two questions. You gave us summary data on the best corrected visual acuity post-op, and the summary statistic is basically 40 percent end with visual acuities worse than 20/40. That was my read on the table, and I just wondered whether that was anticipated, and what were the root cause of these poor acuities in such a large percentage of these patients?

DR. LEPRI: I had addressed that question to the sponsor in one of our deficiency letters that were issued, and the explanation given to me was that many of these patients had severe preoperatively pathologies which would lend then to not have good post-operative visual acuity outcomes.

My contention with that is that there were a large number of patients preoperatively, particularly in the core group, who had BSCVAs that were better than 20/40, and that if they had provided a best case and worst case analysis of